Remarks

Reconsideration of the allowability of the present application is requested respectfully.

Status of the Claims

Claims 1, 2 and 21 to 44 are pending. No claim has been amended, cancelled, or added.

Summary of the Examiner's § 103(a) Rejection

All of the pending claims have been rejected under 35 U.S. C § 103(a) as being unpatentable over the disclosure of British Patent No. 1,564,039 (hereafter "GB '039") in view of the disclosure of Patel et al., *Molecular Pharmacol.*, 46: 943-48 (1994) (hereafter "Patel et al."), and European Application Nos. 0 222 614 and 0 391 369 (hereafter "EP '614" and "EP '369" respectively), and in further view of newly cited Woodruff et al. (see item U in the Examiner's "Notice of References Cited") and U.S. Patent No. 5,224,507 to Dappen et al. (hereafter "Dappen et al.").

It is submitted respectfully that the Examiner's rejection is in error and should be withdrawn for reasons expressed below.

Summary of the Invention

Applicant's claims define a pharmaceutical formulation which comprises an opioid, a CCK antagonist, and a biphasic carrier. The Examiner's attention is directed

to the present application, page 2, lines 7 to 18, which explain the problem which is solved by the provision of applicant's invention, that is, the provision of a system in the form of a biphasic carrier by which a water-soluble opioid and a lipid-soluble CCK antagonist may be delivered simultaneously in applicant's claimed formulation to a patient. The biphasic carrier of the formulation comprises an organic phase which has a solubilising capacity for the CCK antagonist and which includes a glyceride derivative and also a hydrophilic phase.

Introduction to Traversal of Examiner's § 103 Rejection

Let it at once be understood that the Examiner's rejection is on its face weak inasmuch as it is based on the disclosures of six references, a primary reference coupled with the disclosures of five secondary references, and the primary reference does not even refer to the problem addressed by applicant's invention. It is submitted respectfully that the Examiner's rejection involves the use of hindsight (indeed a classic case of hindsight) in which the Examiner has used the disclosure of applicant's specification (not disclosures in the references) to locate the numerous cited publications which are then relied upon by the Examiner in formulating his obviousness rejection. This is, of course, impermissible under the law.

Traversal of the Examiner's §103 Rejection

In the previous Office Action of 29th August 2001, the Examiner asserted that the primary reference (GB '039) discloses the combination of opioids and CCK antagonists. In response to that Action, applicant pointed out that neither the primary reference nor the secondary references disclose delivery of a combination of water-insoluble CCK

antagonists plus water-soluble opioids and, accordingly, the combined disclosures of the cited art do not disclose the combination of a CCK antagonist and an opioid, that is, a combination defined in all of applicant's claims.

In the current rejection, the Examiner has rejected applicant's aforementioned position and has asserted that the newly-cited Woodruff et al. publication identifies certain benzodiazepines as CCK antagonists. In fact, of the three benzodiazepines exemplified specifically in the primary reference (nitrazepam, medazepam and bromazepam), only medazepam is identified by Woodruff et al. as being a CCK antagonist. However, this point is irrelevant to the question of whether the present invention is patentable, as the characterization of a compound as either being or not being a CCK antagonist does not constitute part of the claimed invention.

The heart of the present invention lies in the provision of a system by which water-soluble opioids and lipid-soluble CCK antagonists (species of which are known) may be delivered simultaneously in a formulation which contains them and also a biphasic carrier, the organic portion of which contains a glyceride derivative. The pharmaceutically-active agents themselves are not claimed, only their incorporation into the appropriate phases of the biphasic carrier. The primary reference is silent on biphasic carriers and, therefore, contributes nothing to the skilled worker's hypothetical quest to combine the known ingredients in this way. Furthermore, the primary reference, as pointed out above, does not even mention the problem which is solved by the provision of the present invention.

The following discussion of each of the second references makes it evident that none contains a disclosure which would suggest that its disclosure be combined with the disclosure of the primary reference.

Patel et al.

The Examiner's basis for citing this document seems to be that it teaches that CCK antagonists, such as devazepide, are poorly soluble. This is no more than a statement of one particular problem which the present invention seeks to alleviate, as is stated in the introductory portion of the present application. Again, this reference does not teach a person skilled in the art how to overcome the problem.

EP 0,222,614

The Examiner stated in the previous Action that this reference teaches "a gelatin capsule containing a hydrophobic carrier matrix and a hydrophilic substance which can create channels in the hydrophobic carrier matrix". This analysis of EP '614 is indeed correct; however, the mere creation of channels in the hydrophobic carrier matrix does not constitute a biphasic carrier as defined in the present application. The hydrophobic carrier in this reference is used merely to give sustained delivery of a single water-soluble drug, not a combination of hydrophilic and lipophilic drugs. Accordingly, there is no logical basis whatsoever for combining the disclosure of this secondary reference with that of the primary reference.

Furthermore, the hydrophilic phase disclosed in this reference is present only to promote dispersal or release of the pharmaceutically active agent carried in the hydrophobic phase, not as a carrier for such agents in its own right. In applicant's invention, both phases of the biphasic carrier are used to deliver pharmaceutically-active agents.

Applicant is at a complete loss to understand how one skilled in the art would ever be led to combining the disclosure of this reference with that of the primary reference in view of the substantial differences between the disclosures.

EP 0,391,369

In the previous Action, the Examiner stated that EP '369 discloses a pharmaceutical composition of hydrophobic drugs in the form of oil-in-water emulsions having long term stability. However, as with EP '614, this reference does not disclose the pharmaceutically active agents which are recited in applicant's claims, nor a true biphasic carrier as defined in the claims of the present application. Rather, this reference describes the use of a stable oil-in-water emulsion formulation merely as a means for delivery of a hydrophobic drug; there is no mention of both phases of this system being used simultaneously as a carrier for the combination of pharmaceutically active agents which are defined in applicant's claims.

Woodruff et al.

The Examiner has relied on this newly-cited reference to support his traversal of applicant's previous argument that the benzodiazepines of GB '039 are not (necessarily) CCK antagonists. This point has already been addressed above with the reference to the discussion of GB '039 and, as stated there, is fairly peripheral to the question of patentability. This reference tells the skilled worker nothing about how he or she might combine a CCK antagonist with a water-soluble opioid.

Dappen et al.

The Examiner has cited this new reference to show that gelatin, alginates, cross-linked carboxymethylcellulose and other celluloses, PVP, lactose, and other non-toxic compatible substances are known to be suitable excipients for pharmaceutical dosage forms containing opioids. Althought this is clearly the case, this reference provides little more than a theoretical discussion of a particular field of chemistry and does not disclose pharmaceutical formulations. The possible inclusion of other pharmaceutical agents is mentioned, but it is not stated what these pharmaceutical agents are. Dappen et al. does not teach the skilled worker how to formulate a composition containing a water-soluble opioid and a lipophilic compound.

Conclusion

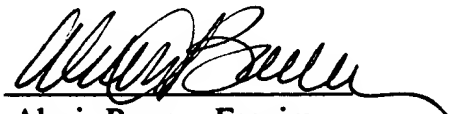
The primary reference was published in 1980. It does not disclose the problem addressed by applicant's invention, that is, how to combine a hydrophilic opioid with a hydrophobic CCK antagonist in a biphasic carrier (as defined in applicant's claims) which enables the simultaneous delivery of both drugs, from both phases, in a single dose. Not one of the secondary references discloses the combination of the drugs recited in applicant's claims and not one of the secondary references even discloses a composition which includes both a hydrophilic drug and a lipophilic drug (let alone the particular classes of drugs recited in applicant's claims). And yet the Examiner advocates that a person skilled in the art would combine the disclosures of the secondary references with the disclosure of the primary reference. Note that these secondary references are a disparate group of publications and consist of a U.S. Journal paper published in 1994, two European patent applications published in 1987 and 1990 respectively, an Abstract from a Journal published in 1991, and a U.S. patent published

in 1993. Again, it is asserted respectfully that the references could have been compiled only with the benefit of hindsight and not by any person skilled in the art who was confronted with the problem identified and solved by applicant.

In view of the above, an early and favorable action is requested respectfully.

This Reply is accompanied by the filing of a "Petition for Extension of Time Under 37 CFR 1.136(a)".

Respectfully submitted,



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